CXCR3 ligands in disease and therapy

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ABSTRACT

Chemokines, binding their various G protein-coupled receptors, lead the way for leukocytes in health and inflammation. Yet chemokine receptor expression is not limited to leukocytes. Accordingly, chemokines are remarkably pleiotropic molecules involved in a range of physiological as well as pathological processes. For example, the CXCR3 chemokine receptor is expressed on activated T lymphocytes, dendritic cells and natural killer cells, but also fibroblasts and smooth muscle, epithelial and endothelial cells. In men, these cells express either CXCR3A, its splice variant CXCR3B or a balanced combination of both. The CXCR3 ligands, activating both receptor variants, include CXCL4, CXCL4L1, CXCL9, CXCL10 and CXCL11. Upon CXCR3A activation these ELR-negative CXC chemokines mediate chemotactic and proliferative responses, for example in leukocytes. In contrast, CXCR3B induces anti-proliferative and anti-migratory effects, as exemplified by angiostatic effects on endothelial cells. Taken together, the unusual and versatile characteristics of CXCR3 and its ligands form the basis for their pertinent involvement in a myriad of diseases. In this review, we discuss the presence and function of all CXCR3 ligands in various malignant, angiogenic, infectious, inflammatory and other disorders. By extension, we have also elaborated on the potential therapeutic applicability of CXCR3 ligand administration or blockade, as well as their additional value as predictive or prognostic biomarkers. This review illustrates the multifunctional, intriguing character of the various CXCR3-binding chemokines.

Keywords: CXCR3; chemokine; G protein-coupled receptor

1. AN INTRODUCTION TO CHEMOKINES

Originally discovered to be chemotactic cytokines leading the way for leukocytes in health and inflammation, the chemokines have now made a name for themselves as pleiotropic molecules involved in a range of physiological as well as pathological processes [1, 2]. Most of their effects are established by signaling through a set of chemokine receptors, typically G protein-coupled receptors (GPCR). Notably, chemokine ligand/receptor binding is both a promiscuous and a redundant interaction, meaning that a particular chemokine will show affinity for several chemokine receptors and a particular chemokine receptor can be activated by various chemokine ligands, respectively. Nevertheless, due to their unique temporal and spatial expression patterns, chemokines often do have non-redundant functions *in vivo* [3]. The biology of chemokines and their receptors is even further complicated by the identification of a set of atypical chemokine receptors (ACKR). Highly related to the classic G protein-coupled chemokine receptors, ACKR are a smaller subgroup of seven-transmembrane receptors, which bind chemokines with high affinity, but do not signal through G proteins [4]. They were originally considered silent scavenger receptors, however, the majority of ACKRs has since been shown to preserve β-arrestin-dependent signaling. Additionally, glycosaminoglycans (GAGs) also influence chemokine function, mostly by retaining chemokines at the endothelial cell surface and presenting them to passing leukocytes that express corresponding chemokine receptors.

The chemokines themselves are small proteins, not bigger than 8 to 10 kDa. They share a common three-dimensional structure defined primarily by four conserved cysteines, two near the amino-terminal tail of the protein, forming disulfide-bonds with two more internal cysteines. A functional distinction is sometimes made between inflammatory and homeostatic chemokines. However, more frequently, chemokine classes are subdivided on the basis of their amino acid sequence homology. Based on the exact configuration of the amino-terminal cysteine pair, a distinction can be made between different subfamilies. The CXC chemokines distinguish themselves from the CC chemokines by the inclusion of a single variable amino acid ‘X’ separating those amino-terminally located cysteine residues. Together, the CC and CXC subfamilies constitute the majority of chemokines, whereas the C

and CX_3C chemokines represent a limited number of rather unconventional chemokines. Though seemingly limited by the constraints of a highly conserved structure, the chemokines are without a doubt a diverse superfamily. This certainly also applies to the subfamily of CXC chemokines, which has gained extra attention because of its role in the regulation of angiogenesis, the formation of new blood vessels, branching of a pre-existing vascular network [5, 6]. Interestingly, a conserved ELR-motif, consisting of a glutamic acid, leucine and arginine, often precedes the most amino-terminal cysteine. The presence of this motif appears crucial in determining the chemokine's biological function as it defines receptor-binding [7]. All ELR-positive CXC chemokines bind the CXCR2 receptor, expressed on leukocytes, such as neutrophils, and on endothelial cells [8, 9]. Accordingly, the ELR-positive CXC chemokines attract neutrophils and promote angiogenesis, respectively. The ligands of CXCR1 also contain an ELR-motif and are particularly potent neutrophil chemoattractants. On the other hand, CXC chemokines lacking the ELR-motif are unable to bind CXCR2. For example, CXCL12/stromal cell-derived factor-1 (SDF-1) alternatively binds CXCR4 and ACKR3/CXCR7, receptors to which pro-angiogenic effects have been attributed as well [10]. However, most ELR-negative CXC chemokines bind the CXCR3 receptor, as do CXCL4/platelet factor-4 (PF-4), CXCL4L1/PF-4var, CXCL9/monokine induced by interferon-γ (Mig), CXCL10/interferon-γ-induced protein-10 (IP-10) and CXCL11/interferon-inducible T cell α chemoattractant (I-TAC) (Figure 1) [11-15]. As opposed to CXCR2, this CXCR3 receptor has been ascribed angiostatic properties, specifically its splice variant CXCR3B, a variant expressed on endothelial cells [11].

The CXCR3 ligands thus represent a distinct group of angiostatic chemokines, besides also retaining their classic chemotactic potential as they additionally direct migration of CXCR3A-expressing lymphocytes to sites of inflammation. Most CXCR3 ligands also bind several GAGs, despite considerable differences in affinity among these chemokines [15-17]. They thus compete with various angiogenic growth factors, such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (FGF2), for binding to GAGs on the proteoglycans presented on the endothelial cell surface. Consequently, CXCR3 ligands hinder binding of these growth factors to their respective signaling receptors [18]. As indicated by recent studies, additionally, direct proteoglycan-mediated

signaling seems increasingly plausible. Indeed, GAG-binding has been held accountable for effects of CXCL4 on monocytes and neutrophils [19-22].

2. CXCR3 AND ITS LIGANDS

2.1. The CXCR3 receptor

The CXCR3 receptor is a seven-transmembrane GPCR, classified as a CXC-type receptor based on the structure of its chemokine ligands. This receptor was indeed originally cloned and characterized as an activated T lymphocyte-expressed GPCR selective for ELR-negative CXC chemokines CXCL9 and CXCL10 [13]. In contrast to other chemokine receptors, the human CXCR3 gene was allocated to the X chromosome, in the q13 region [23]. In culture, the percentage of CXCR3-positive T lymphocytes has been shown to increase upon interleukin (IL)-2 or IL-2/phytohemagglutinin (PHA) stimulation, resulting in up to 95% receptor-expressing cells [23]. T lymphocyte activation accordingly induces cell responsiveness to CXCR3 ligands. A heterogeneous group of effector T lymphocytes, including CD4+ T helper (Th) cells, CD8+ cytotoxic T lymphocytes (CTL), as well as memory T cells, either CD4+ or CD8+, show highly increased expression of CXCR3 in contrast to their naïve precursors [24, 25]. However, among the Th cell population, CXCR3 would particularly mark Th1 cells, rather than Th2 or Th17 cells [24, 26]. The transcription factor T-bet, a master switch for Th1 and CTL commitment, directly promotes CXCR3 expression [27, 28]. Interestingly, IFN-γ signaling, via T-bet, also promotes CXCR3 expression on a subset of Th1-specific regulatory T cells [29]. Additionally, natural killer (NK) cells were demonstrated to express CXCR3 [13]. Functional expression of CXCR3 was also demonstrated on dendritic cells [15, 30]. CXCR3 ligands have a broad spectrum of biological activities, acting on various CXCR3-expressing cell types. Though CXCR3 expression among immune cells is restricted, with no detectable expression on resting T lymphocytes, B lymphocytes, monocytes or granulocytes, a wide variety of non-immune cells have in fact been shown to express and display CXCR3 as well, including fibroblasts, endothelial, epithelial and smooth muscle cells [31]. These cells do display a variable, cell-dependent expression pattern of different human CXCR3 splice variants. Most cells, including leukocytes, predominantly express the originally identified CXCR3A. CXCR3A consists of 368 amino acids, encoded by just two exons, separated by a

single intron, and couples to a $G_{\alpha i}$ which mediates pro-migratory and proliferative signaling and increases intracellular calcium levels [11, 13, 23]. In contrast, endothelial cells exclusively express the splice variant CXCR3B, which instead couples to a $G_{\alpha s}$ subunit, initiating opposing signaling cascades [11]. CXCR3B is a 415 amino acid long receptor, generated by alternative splicing at the 5' end of the second exon. Additionally, the inserted sequence comprises an alternative start codon resulting in the loss of the four most amino-terminal residues encoded by the first exon, which are replaced by a new amino-terminal tail of 51 amino acids. Most CXCR3A-positive cells do exhibit low, parallel expression of CXCR3B. Existence of two presumably functionally divergent variants can explain the angiostatic effect attributed to CXCR3 ligands. No alternative splicing of the CXCR3 receptor was identified in mice, though murine CXCR3 on endothelial cells does exhibit CXCR3-mediated angiostatic effects [15]. A cell-dependent signaling mechanism could be involved, establishing differential G protein-coupling, independent of CXCR3 splicing. Different intracellular domains of the receptor have been shown to determine functional activity, in a ligand-dependent manner [32, 33]. The different domains are also of varying importance in establishing distinct, parallel downstream effects. However, the determinants of splice variant-dependent differential CXCR3 G protein-coupling remain thus far enigmatic. Furthermore, a third human splice variant generated by exon skipping, named CXCR3-alt, was later identified [14]. CXCR3-alt consists of only 267 amino acids. This variant shows considerable structural and functional dissimilarities attributed to a frame-shift. Only four transmembrane domains are conserved and a fifth domain within the alternative carboxy-terminal sequence has been postulated [14]. Despite drastically deviating from the classic seven transmembrane CXCR3A conformation, CXCR3-alt surprisingly retains affinity for CXCL11, whereas no other CXCR3 ligands are bound (Figure 1). Though affinity is lowered, CXCL11 can evoke a CXCR3-alt-mediated modest calcium increase and chemotactic response [14, 34].

Study on altered, chimeric CXCR3/CXCR1 receptors has taught that several distinct extracellular domains of human CXCR3A collectively ensure efficient ligand binding and following receptor activation, proposing a so-called multi-site model of ligand/receptor interaction [35]. CXCR3's amino-terminal tail and first extracellular loop, though dispensable for CXCL9-induced activation, both play

a more important role in CXCL10- and CXCL11-mediated activation. In fact, sulfation of two tyrosine residues in the amino-terminus of CXCR3A was later described to be a necessity for binding and activation by all three chemokines [36]. In line with earlier findings, this report did, however, also demonstrate CXCL10 and CXCL11 receptor binding to be more sensitive to amino-terminal truncation of the receptor compared to CXCL9 [36]. The second extracellular loop of CXCR3A, and in particular an arginine at position 216, proved crucial for receptor activation by all interferon (IFN)-γ-inducible chemokines [35, 36]. Surprisingly though, R216 is no absolute requirement for ligand/receptor binding nor CXCR3 internalization. Finally, CXCR3A's third extracellular loop appears necessary for CXCL9 and CXCL10 function [35]. In general, CXCL11 is suggested to be more tolerant to substantial changes within the extracellular loops. Accordingly, CXCL11 is indeed the only CXCR3 ligand known to induce CXCR3-alt-mediated signaling, as mentioned earlier [14].

Note that past research solely focused on the amino acid sequence and structure of splice variant CXCR3A, disregarding the binding properties of CXCR3B. The amino-terminal elongation of CXCR3B and the associated shift in affinity towards different CXCR3 ligands, can be reconciled though with the postulated multi-site model and the reported impact of amino-terminal changes on ligand binding. Beyond the altered 51 amino acid long amino-terminal tail, both splice variants are identical. Presumably, other findings on the structure and function of CXCR3A can thus be extended to CXCR3B.

Among the CXCR3-binding chemokines, two groups clearly can be distinguished based on their overall biology and biochemistry (Table 1). On one hand, the IFN-γ-inducible chemokines CXCL9, CXCL10 and CXCL11 constitute the traditional CXCR3 ligands. The platelet-derived chemokines CXCL4 and CXCL4L1, on the other hand, were only later recognized to bind both CXCR3A and CXCR3B as well and represent a distinct pair of CXCR3 ligands.

2.2. IFN-γ-inducible CXCR3 ligands

Three ELR-negative CXC chemokines, CXCL9, CXCL10 and CXCL11, can together be referred to as the IFN-γ-inducible CXCR3 ligands [12, 37, 38]. Though they share a common inflammatory

function, they do collectively gain fine control over leukocyte trafficking [3]. The mature IFN-γ-inducible chemokines display about 40% amino acid sequence identity between one another (Figure 2). However, the expression of CXCL9, CXCL10 and CXCL11 is regulated by unique promoters establishing distinct temporal and spatial expression patterns (Table 1). They are indeed differentially expressed by various cell types, induced by specific cytokines and Toll-like receptor (TLR) ligands or by combinations thereof [3, 39-41]. Furthermore, these chemokines all exhibit different receptor binding characteristics, different efficacy as well as potency. Generally, CXCL11 has the highest affinity for CXCR3A, whereas CXCL9 has the lowest. CXCL11 is also the most potent of the IFN-γ-inducible CXCR3 ligands, as measured by both mobilization of intracellular calcium and chemotactic response in CXCR3A-expressing cells [12]. However, CXCL10 expression appears more receptive to a range of different stimuli and has been associated accordingly with a multitude of physiological as well as pathological conditions [3]. CXCL10 is the most thoroughly investigated CXCR3 ligand and could be suggested a prototypical example of the IFN-γ-inducible chemokines.

2.3. Platelet-derived CXCR3 ligands

The mature chemokines CXCL4 and CXCL4L1 both show 37% sequence identity with the IFN-γ-inducible CXCR3 ligand CXCL10 (Figure 2). However, among themselves, these non-allelic variants show a striking 96% amino acid identity. CXCL4L1 is a non-allelic variant of CXCL4 which arose from a gene duplication unique to primates [42]. Only three amino acid substitutions near the carboxy-terminal end distinguish the mature chemokines. Yet this subtle difference suffices to alter the chemokine's three-dimensional structure drastically, reducing CXCL4L1's affinity for GAGs and resulting increased angiostatic potential of the variant CXCL4L1 [42, 43].

On the other hand, CXCL4 and CXCL4L1 clearly differ from the other CXCR3 ligands firstly based on their affinity for CXCR3A and CXCR3B, but also because their expression is not classically induced by IFN-γ. Even more, they are primarily released by activated platelets, therefore coined as the platelet-derived CXCR3 ligands [43, 44].

3. CXCR3 LIGANDS IN DISEASE

Given their pleiotropic nature, CXCR3 ligands play their part in a myriad of diseases. Involvement of all CXCR3 ligands has been observed in various angiogenesis-related pathologies as well as immunological disorders, the latter being mostly related to autoimmunity or infection [45, 46]. Here we discuss a varied and extensive, yet not exhaustive, repertoire of diseases having been associated with CXCL4, CXCL4L1, CXCL9, CXCL10 or CXCL11. The CXCR3 ligands are indeed characterized by their unique position at the crossroad of immunity and angiogenesis and accordingly play an exceptional role in health, disease and therapy.

3.1. Carcinoma and sarcoma

The CXCR3 ligands have been associated with many diseases, some new and still poorly understood, some already the subject of a long line of research. Their association with the pathogenesis and prognosis of cancer definitely belongs to the latter. The immunoangiostatic CXCR3 ligands are established players in numerous carcinomas and sarcomas [47]. Angiogenesis is indeed a critical process providing the expanding malignant tissue with oxygen and nutrients and clearing it of metabolic waste products [48, 49]. While these newly formed blood vessels allow successful tumor growth, the lymphatic vasculature will serve as an additional escape route for metastatic tumor cells, especially in later stages of tumor progression [50]. Recent reports reveal that CXCR3 ligands, specifically the platelet factors, are effective inhibitors of lymphangiogenesis as well [51] and hence support the belief that these chemokines are interesting, multifunctional anti-tumoral agents (Figure 3).

Furthermore, immunity also plays an ambiguous role. Generally, the tumor is believed to corrupt the immune system and suppress any anti-tumoral reactivity, possibly even attracting immune cells that will further promote tumor vascularization [52]. In contrast, immune polarization of the tumor microenvironment could potentially stimulate the anti-tumoral immune response, attracting CXCR3A-expressing, anti-tumoral CTLs, activated Th1 lymphocytes and NK cells [53]. It is no wonder that several chemokines, being immunological players attributed both angiogenic and angiostatic properties, also play their part in tumor development [45]. An abundance of studies have reported

overexpression or absence of CXCR3 ligands, especially CXCL10, in cancer patients [47, 54]. Despite a broad understanding of their potential anti-tumoral activity, the associated clinical significance often remains enigmatic. The impact of CXCR3 ligands on both tumor and tumor microenvironment is further complicated by some tumors' ability to express the CXCR3 receptor. CXCR3 expression was illustrated in many different cancers, formerly without distinguishing CXCR3A from CXCR3B [55-58]. Given tumoral $G_{\alpha i}$-coupled CXCR3A surface expression, CXCR3 ligands will stimulate tumor cell migration and proliferation thereby promoting tumor invasiveness (Figure 4) [59]. CXCL4 and CXCL10 were accordingly reported to promote the metastatic potential of human, predominantly CXCR3A-expressing, prostate cancer cells *in vitro* [59]. In several other cancers, tumoral expression of CXCR3 was also associated with lymph node invasion or generally poor prognosis [60-62]. While mostly considered anti-tumoral agents, CXCR3 ligands can thus also have a detrimental, pro-tumoral effect under certain conditions. These findings require careful consideration to assure safe and efficient future therapeutic applicability. The impact of individual differences in tumoral CXCR3A and CXCR3B expression demands a personalized approach.

3.2. Leukemia, lymphoma and myeloma

Leukemia, lymphoma and myeloma, collectively referred to as hematopoietic malignancies, represent a rather unique set of cancers affecting leukocytes and their progenitors. All three diseases can be further divided into subclasses. As for leukemia, a distinction is made between acute or chronic, and lymphoid or myeloid disorders. Interestingly, the CXCR3 receptor and its ligands have been discussed in the context of all four major subtypes. In chronic lymphocytic leukemia (CLL), the CXCR3-signaling axis has mostly been linked to trafficking of CLL malignant B cells, which consistently express functionally active CXCR3, unlike B cells isolated from healthy subjects [63, 64]. CLL cells themselves were also frequently observed to co-express CXCL9 [64]. Furthermore, CXCL9, CXCL10 and CXCL11 were identified as part of an outcome-correlated cluster of cytokines, differentially expressed in CLL, with elevated serum levels serving as an indication of aggressive disease [65]. The cluster additionally consisted of CCL3, CCL4, CCL19, IL-5, IL-12 and IFN-γ. On the other hand, low levels of CXCR3 expression by CLL B cells have previously been reported to predict a poor outcome

and shorter survival as well [66]. In acute lymphoblastic leukemia (ALL), CXCL10 produced by monocytes in the vicinity of malignant blasts was hypothesized to have a direct pro-tumoral effect promoting tumor cell invasiveness [67]. CXCL10 serum levels in ALL patients were also proven to be increased compared to controls [68]. In contrast, decreased serum levels of another CXCR3 ligand, CXCL4, were discovered to characterize pediatric ALL [69]. Remarkably, involvement of CXCL4 in the oncogenesis of ALL was strongly supported by the identification of a translocation shared among a subset of ALL patients, with a breakpoint in 4q21, distal to the CXCL4 gene [70, 71]. Similarly, in acute myeloid leukemia (AML) CXCL4 serum levels were decreased as well, yet progressed in relation to therapy responsiveness, with increasing concentrations indicating AML remission [72, 73]. On the other hand, AML cells often constitutively produce CXCL10, with wide variations between patients potentially reflecting disease status [74]. Considering chronic myeloid leukemia (CML), a fourth leukemic subtype, CXCL10 mRNA levels were just recently reported to be upregulated in peripheral blood mononuclear cells isolated from CML patients, linking CXCR3 ligands to the pathogenesis of CML as well [75]. Dysregulation of CXCL10 gene expression has in fact been associated with several recurrent chromosomal translocations identified in different leukemic pathologies [76].

Hodgkin's lymphoma tissue also generally presents higher levels of CXCL9 and CXCL10 expression, though major differences are noted among different subtypes with predominant expression in Epstein-Barr virus (EBV)-positive cases and cases associated with mixed cellularity [77, 78]. Both chemokines were shown to be expressed by malignant cells as well as surrounding cells such as macrophages, lymphocytes and endothelial cells. This overexpression of both CXCL9 and CXCL10 has actually been associated with tumor tissue necrosis and vascular damage, consistent though with their general anti-tumoral activity. This duality was also illustrated in non-Hodgkin lymphoma, with on one hand reports of CXCL9 expression in B-cell lymphomas facilitating dissemination of CXCR3-positive malignant B cells [79-81] and on the other hand the suggestion that CXCL9 and CXCL10 are in fact associated with a protective immune response successfully targeting B cell cancer, comparable to their anti-tumoral activity reported in solid tumors [82].

Finally, for most multiple myeloma (MM) cases, freshly purified MM plasma cells have been shown to express CXCR3, making them responsive to chemokines like CXCL9, CXCL10 and CXCL11 [83]. Remarkably, myeloma cells express both CXCR3 splice variants, at varying ratios and in a cell cycle-dependent manner, potentially explaining the reported anti-proliferative effect of CXCL10 [84, 85]. As for CXCL4, shown to induce apoptosis of myeloma cells, this platelet factor was identified as tumor suppressor gene commonly silenced in MM as a consequence of promoter hypermethylation [86, 87].

In conclusion, most hematological cancers have, in one way or another, been linked to CXCR3 ligand expression. However, seldom their exact pathological or oncogenic function is really understood. This is a domain that requires further research, especially considering the prospects for leukemia patients and the shortcomings of current treatments. CXCL4 in particular appears to present promising new therapeutic opportunities as this chemokine may also serve to protect normal hematopoietic cells from the toxicity of chemotherapeutics, without affecting the viability of cancerous cells [88].

3.3. Inflammatory arthritis

Over the years, CXCR3 ligands and their function in autoimmune diseases such as rheumatoid arthritis (RA) have been extensively reported and reviewed [89]. In RA patients, recruitment of CXCR3-expressing T cells and mast cells to the inflamed synovium was indeed related to a preferential upregulation of CXCL9 and CXCL10 expression in the synovial fluid and tissue compared to chemokine levels in traumatic arthritis or osteoarthritis [90, 91]. This association was later also extended to enhanced CXCL4 expression concurrently with synovial inflammation in RA [92]. Elevated CXCL4 plasma levels have also been observed in a subset of RA patients, specifically concurrent with the formation of active vascular lesions [93]. Plasma CXCL4 concentrations might indeed prove to be a useful marker of endothelial injuries in rheumatic disorders [93]. Furthermore, synovial CXCL10 expression was also found to be increased in juvenile idiopathic arthritis [94]. Also in septic arthritis, inflammatory induction of CXCL9 and CXCL11 has been reported [41]. However, clearly distinguishing itself from other IFN-γ-inducible chemokines, evidence regarding increased secretion of CXCL11 in RA remains controversial [39, 95]. High synovial expression of CXCL11 in a

particular subpopulation of RA patients has, however, been identified as an indication of poor therapy responsiveness to adalimumab, a TNF-antagonist [96].

3.4. Inflammatory bowel disease

The CXCR3 axis has been implicated in the pathogenesis of both Crohn's disease and ulcerative colitis, two chronic gastrointestinal disorders collectively referred to as inflammatory bowel disease (IBD) [97, 98]. Raised plasma levels of CXCL4 were observed in Crohn's disease already in 1987 [99] and were furthermore correlated with IBD clinical activity [100]. Serum CXCL4 has more recently also been identified as a general biomarker for IBD in a proteomic serum profiling pilot study [101]. Though serum CXCL10 levels were also suggested to reflect disease activity in ulcerative colitis [102], expression of IFN-γ-inducible CXCR3 ligands has mostly been found to be increased locally, driving mucosal accumulation of inflammatory cells [97, 103, 104]. Accordingly, it has been suggested that these IFN-γ-inducible chemokines could contribute to the progression of IBD and worsen the associated inflamed state of the gastrointestinal tract [104, 105]. Involvement of the CXCR3 axis genes was supported by the report of a persistent overexpression of CXCL9, CXCL10, CXCL11 and CXCR3 in the inflamed colonic tissue of pediatric IBD patients [106]. A particular CXCL11 genotype, namely the rs6817952 A allele situated in intron 1, even proved to be a risk factor for both ulcerative colitis and pediatric Crohn's disease [106]. In a similar report, a CXCL9 polymorphism, 77147452G>A, showed an inverse association with pediatric Crohn's disease [107]. These genetic association studies underline the importance of the CXCR3 receptor and its ligands in the pathogenesis of IBD and could inspire new therapeutic strategies.

3.5. Diabetes

As an autoimmune disease, type 1 diabetes has repeatedly been associated with elevated levels of the typical Th1 chemokine CXCL10, a correlation unveiled by Shimada and colleagues and reassessed earlier this year by the group of Antonelli *et al.* [108, 109]. It is further hypothesized that CXCL10 serum levels would increase especially during the early Th1-driven stages of disease [110, 111]. However, there is also a minority of studies contesting this positive association between serum

CXCL10 and type 1 diabetes [112, 113]. Nevertheless, generally it is accepted that hyperglycemic and inflammatory CXCL10 production plays an important role in the pathogenesis of type 1 diabetes [114-116]. While monocytes are an important source of the chemokine, pancreatic beta cells in patient biopsies were actually shown to express and secrete CXCL10 themselves as well, contributing to autoreactive T cell islet infiltration and consequent beta cell destruction [117-119]. Potentially, beta cell-secreted CXCL9 may also attract CXCR3-expressing T cells [120]. Through TLR4 signaling, CXCL10 has even been described to interfere directly with pancreatic beta cell proliferation and viability, an effect originally assumed to be mediated by CXCR3 expressed on pancreatic beta cells [121-123]. Regardless of the controversy concerning involvement of CXCR3 itself, this direct effect on pancreatic beta cell numbers implicates CXCL10 not only in the progression of type 1 but also of type 2 diabetes, as a lack of proliferation prevents beta cells from meeting increased insulin demands, for example in obese or pregnant patients [122]. Accordingly, the latter study indeed showed that in type 2 diabetes patients, unlike healthy controls, pancreatic beta cells also express and secrete CXCL10.

Though not always clear-cut, several studies have investigated the association between platelet activation and coagulation factors on one hand and diabetes on the other. This also led to the observation that diabetic patients present increased CXCL4 plasma levels, presumably related to enhanced platelet activation [124, 125]. Like most CXCR3 ligands, CXCL4 has been studied regarding its involvement in complications of diabetes, such as proliferative diabetic retinopathy (PDR) [125, 126]. Characterized by distorted, pathological neovascularisation of the retina, several angiogenic factors have been shown to have a causative link to this pathology. But the distorted angiogenic balance in the diabetic eye also affects the angiostatic proteins involved, showing a counterintuitive upregulation of inhibitors of angiogenesis such as the CXCR3 ligands [127]. Chemokine concentrations measured in the vitreous fluid of patients correlate to clinical PDR manifestation. For example, vitreous CXCL9 levels have been shown to be elevated in patients with active PDR, but not in patients with inactive PDR [126]. A causal role for the CXCR3 ligands in this

severe complication in diabetes patients may remain enigmatic, but their potential as disease markers is apparent as is their potential therapeutic applicability.

3.6. Systemic sclerosis

Proteome-wide analysis recently revealed circulating and dermal plasmacytoid dendritic cells isolated from systemic sclerosis (SSc) patients to display markedly increased CXCL4 expression [128]. This study also confirmed plasma CXCL4 levels to be elevated, as had been previously described [129, 130]. More importantly, plasma levels of CXCL4 correlated with disease severity, specifically the presence and progression of complications such as pulmonary arterial hypertension and lung or skin fibrosis [128]. Increased CXCL4 levels had previously been measured in the bronchoalveolar lavage fluid of SSc patients [131]. Similarly, serum concentrations of the IFN-γ-inducible CXCR3 ligand CXCL10 appear indicative of disease activity [132]. Increased serum CXCL10 levels also correlate with the manifestation of pulmonary arterial hypertension [133]. In general, increased serum levels of CXCL9 and CXCL10 have been described consistently in SSc patients [134-136]. In contrast, low concentrations of CXCL11 in the lung have been associated with a greater likelihood of pulmonary function decline [137].

3.7. Transplant rejection

As potent T cell-chemoattractants, CXCL9 and CXCL10 have been demonstrated repeatedly to play a central role in the immune response against transplant tissue, leading to allograft rejection [138, 139], despite a few reports opposing involvement of the CXCR3 axis [140]. Regulating immune cell differentiation, migration and proliferation, local chemokine levels indeed closely relate to the host immune status, both pre- and post-transplantation [141-144]. Upregulation of CXCL10 expression, potentially serving as a biomarker predicting allograft failure, is indeed reflected by chemokine concentrations in serum and urine [139, 145], as is CXCL9 expression according to some studies [146]. These findings have been reported in various organs, including the transplanted kidney, lung, heart and liver [147-153]. Similar to CXCL9 and CXCL10, the third IFN-γ-inducible chemokine, CXCL11, has been observed to be upregulated in a number of transplant studies [151, 152, 154, 155].

As measured in endomyocardial biopsies, a persistent elevation in CXCL10 and CXCL11 mRNA expression was found to correlate with the occurrence of transplant vasculopathy, a severe complication among heart transplant recipients causing allograft ischemia [156].

A murine study also associated CXCL4 with allograft rejection in the context of cardiac transplantation. However, CXCL4 was actually considered a negative regulator of T cell reactivity to cardiac transplantation, by limiting Th17 differentiation [157].

CXCR3-binding chemokine levels have also been associated with patient prognosis after bone marrow transplantation, more specifically in the context of graft-versus-host-disease (GVHD), a complication in which transplanted donor cells regard the host tissue as foreign. The importance of CXCL10 in the pathogenesis of this disease was first recognized in acute GVHD, characterized by epidermal CXCL10 expression and recruitment of CXCR3-positive T cells to the skin [158]. Serum levels of this chemokine were significantly increased during acute GVHD. Furthermore, serum levels of all three IFN-γ-inducible CXCR3 ligands, CXCL9, CXCL10 and CXCL11, also correlated to episodes of chronic GVHD of the skin [159]. Correspondingly, during ocular manifestation of chronic GVHD, increased expression of CXCL9 and CXCL10 has been observed within the conjunctiva [160]. These observations thus suggest a central role for the CXCR3 ligands in the pathogenesis of both acute and chronic GVHD.

3.8. Malaria

The role of platelets in malaria, and with it a potential involvement of the platelet-specific protein CXCL4, has been recognized early on [161, 162]. In 1983, Essien and Ebhota described elevated CXCL4 plasma levels in patients upon acute *Plasmodium falciparum* infection [163]. On the other hand, the IFN-γ-inducible CXCR3 ligands were later implicated in the pathogenesis of malaria as well. Most importantly, the CXCR3 ligands have been associated with the occurrence of cerebral malaria (CM), a lethal complication of *Plasmodium falciparum* infection in humans [164, 165]. Aspiring to identify prognostic markers that may predict CM severity and hopefully improve intervention, CXCL10 and CXCL4, in contrast to CXCL9 or CXCL11, were found to be exceptional serum markers

associated with CM mortality [166, 167]. Following up on the potential value of CXCL10 in predicting CM associated mortality, a specific CXCL10 gene promoter polymorphism -1447A>G, associated with higher plasma CXCL10 levels, was identified as a genetic risk factor predicting clinical severity of malaria and susceptibility to CM [168]. The hypothesized key role for CXCL10 in cerebral malaria was further supported by preclinical data illustrating that this chemokine promotes accumulation of CXCR3-positive T lymphocytes in the brain, an essential part of the pathogenesis of CM [165, 169-171]. In parallel to CXCL10, a prominent role for CXCL4 in the pathogenesis of fatal CM was suggested as well [167]. Murine CXCL4 contributed to the vascular inflammation, driving both T cell and monocyte trafficking, which consequently leads to cerebral vascular injury typical of the development of experimental CM [172, 173]. Despite the lack of an identified correlation in patients, preclinical studies have also connected CXCL9 to this severe complication [174-177]. Moreover, in murine models of CM, CXCR3 expression or in contrast lack thereof has been associated with susceptibility to or protection against fatal murine CM, respectively [165, 169, 170, 176]. Protection goes hand in hand with a reduction of T lymphocyte recruitment in response to the IFN-γ-inducible CXCR3 ligands excessively expressed in the brain [170]. Neutralisation of CXCL10 in mice inhibits the recruitment of T cells from the spleen to the brain, thereby preventing cerebral inflammation and improving parasite clearance in the spleen [171]. In contrast, the protective, antimalarial effect of CXCL4 can be traced back to its remarkable quality to bind the Duffy-antigen receptor for chemokines (ACKR1/DARC) expressed on erythrocytes [178-180]. Activated platelets, bound to malaria-infected red blood cells, will locally release high concentrations of CXCL4, which in turn binds DARC leading to intraerythrocytic parasite-killing [179, 181, 182].

3.9. Acquired Immune Deficiency Syndrome

Serving as co-receptors for cell-specific human immunodeficiency virus (HIV) entry, CCR5 and CXCR4, as well as several other chemokine receptors, have been identified as critical pawns in HIV infection and pathogenesis, eventually leading to acquired immune deficiency syndrome (AIDS) [183, 184]. Though it was demonstrated that CXCR3 is also a potential co-receptor, given its marginal co-receptor efficiency, clinically CXCR3 is unlikely to take significant part in the process of HIV

infection [185]. On the other hand, the receptor and its ligands do play a role in the progression of this disease, even though it may not yet be entirely clear what that role entails.

Firstly, plasma levels of CXCL10 were recently suggested as a marker to predict viral load [186, 187]. Furthermore, CXCL10 has been detected in the cerebrospinal fluid (CSF) of HIV-1-infected patients, driving the accumulation of activated T cells and accordingly contributing to the occurrence of HIV-associated disorders of the central nervous system [188-190]. It was indeed repeatedly shown that a variety of cells, including dendritic cells, macrophages and lymphocytes but also astrocytes and microglia, can express significant amounts of CXCL9, CXCL10 and CXCL11 following HIV-infection [191-195]. Notably, CXCL10 was also identified as a direct neurotoxic factor [196, 197]. Most importantly, recruitment of susceptible CXCR3-expressing T cells to virus-infected macrophages, dendritic cells and lymph nodes is favored, ensuring ongoing propagation of the virus in newly supplied target cells and inflicting the general immunopathology of AIDS [192, 198]. Interestingly, the CXCR3 ligands also have a more direct impact on HIV infection as CXCL9, CXCL10 and CXCL11 were all shown to stimulate virus replication in a CXCR3-dependent manner [199].

Similar to the other CXCR3 ligands, CXCL4 also affects the pathogenesis of HIV. Remarkably, CXCL4 is believed to interfere specifically with the earliest events in the viral infectious cycle and would actually be a key player in the first line defense against HIV-1 [200, 201]. Activated platelets inhibit host cell entry by HIV through the release of CXCL4, which behaves as a broad-spectrum inhibitor, directly interacting with the major viral envelope glycoprotein, gp120, and thereby suppressing attachment and entry [200]. Unlike the other CXCR3 ligands, CXCL4 thus would be ascribed a protective role, supported by an inverse correlation between CXCL4 serum levels in HIV-1-infected patients and the clinical stage of their disease [200].

On a side note, CXCR3 ligands also seem to be involved in opportunistic infections manifesting in HIV-positive patients. In this context, the IFN-γ-inducible chemokines, especially CXCL10, have been linked to hepatitis C [202-205], tuberculosis [206, 207] and even malaria [208].

3.10. Hepatitis

In general, CXCR3-binding chemokines have been ascribed direct antimicrobial activity, mostly directed towards bacteria and malaria parasites [178, 182, 209, 210]. However their involvement in leukocyte recruitment and differentiation places the CXCR3 ligands at the front line of the host defense against different infectious diseases, including viral infections of the central nervous system [211, 212]. A link was also established between the IFN-γ-inducible chemokines and viral hepatitis, mostly hepatitis C [213]. However, the hepatitis C virus (HCV) can modulate the chemokine system, upregulating inflammatory chemokines yet subverting a specific immune response, postulated to result in the establishment of chronic low-grade inflammation and an impaired viral clearance [213, 214]. Both CXCL9 and CXCL10 have been reported to facilitate accumulation of T lymphocytes in the infected liver leading to patchy lobular inflammation, an important predictor of progressive liver injury [215-217]. Elevated CXCL10 plasma levels indeed mark hepatitis C patients with advanced fibrosis, whereas CXCL9 levels according to some studies mostly associate with advanced inflammation [218]. It has even been reported that CXCL9 may exert antifibrotic effects [219]. Additionally, Sahin and colleagues recently suggested CXCL10 has a direct pro-apoptotic effect on hepatocytes as well, potentially contributing to CXCL10-associated liver injury [220].

CXCL11 is also expressed by hepatocytes in chronic hepatitis C and promotes recruitment of pro-inflammatory T cells and subsequent portal and lobular inflammation [221]. Its intrahepatic expression may be mildly elevated in chronic hepatitis C patients with higher necroinflammation and fibrosis [222].

Finally, Zaldivar and colleagues revealed that patients with advanced HCV-induced fibrosis present increased CXCL4 serum concentrations and intrahepatic CXCL4 mRNA levels [223]. Also in non-viral, alcoholic hepatitis, increased expression of CXCL4 and CXCL10 in patient liver biopsies was reported [224]. Similarly, elevated serum concentrations and intrahepatic expression levels of CXCL9 and CXCL10 were shown to be positively associated with severity of liver fibrosis in chronic liver diseases of different etiologies, viral or otherwise [225].

3.11. Atherosclerosis

The initiation and progression of atherosclerosis, an arterial narrowing caused by the formation of progressive and degenerative plaques, is fundamentally intertwined with the chemoattraction and modulation of immune cells, most importantly monocytes and lymphocytes. Activated T lymphocytes accumulate in the atheroma early on, recruited at least in part by locally expressed CXCL9, CXCL10 and CXCL11 [226]. Different studies have indeed highlighted the effect of these chemokines on lesional T cell infiltration and as such on the consequent progression of atherosclerotic plaques [227-229]. On the other hand, CXCL4 differs from the others in that this chemokine mostly retains peripheral monocytes at the lesion site, where this proatherogenic chemokine is released at high concentrations following platelet activation [230]. Heterodimerization of CXCL4 with another platelet chemokine, CCL5/RANTES, even further enhances monocyte recruitment [231]. As reviewed by Aidoudi and Bikfalvi, many diverse regulatory mechanisms are involved in the achieved impact of CXCL4 on the progression of atherosclerosis [232]. CXCL4 instigates local monocyte differentiation to macrophages and controls their polarization [22, 233]. Remarkably, this platelet factor also modulates the low-density lipoprotein (LDL) cholesterol metabolism by inhibiting degradation of the LDL-receptor. CXCL4 simultaneously prevents native LDL to bind to its receptor, but selectively promotes the macrophage's uptake and following esterification of oxidized LDL, a crucial step in the development of foam cells which form the basis for future atherosclerotic plaques [232-234]. Accordingly, lesional CXCL4 deposition is shown to correlate with the clinical manifestation of atherosclerosis [235]. This enforces the hypothesis that CXCR3 ligands, though each via specific mechanisms, collectively contribute to the progression of atherosclerosis to a symptomatic disease [227, 235, 236].

3.12. Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disorder in which deposition of neurotoxic β-amyloid peptides, forming senile plaques, as well as formation of neurofibrillary tangles cause brain lesions leading to severe dementia [237]. Typically, AD patients also present with neuroinflammation. The physiological role of chemokines and their receptors in the brain has been established before, but

even more so are they considered to be associated with the pathogenesis of various neurological diseases, including AD [238]. Reactive astrocytes in AD were reported to display elevated CXCL10 expression and CXCL10- as well as CXCL9-induced signaling was confirmed in CXCR3-expressing neurons [239]. These findings were corroborated by reports of CXCL10-mediated calcium dysregulation and apoptosis in neurons, and thus neurotoxicity [240]. CXCL10 has also been reported to regulate migration of astrocytes themselves thereby promoting astrocyte aggregation around senile plaques [241]. Furthermore, CXCL10 concentrations in the CSF, as opposed to serum levels, were increased in AD patients, specifically during the early phase of disease, characterized by a mild cognitive decline and typically associated with more pronounced inflammatory events [242-244]. Increased CXCL10 expression was also observed in the brain of transgenic AD mice in which colocalization of β-amyloid and CXCL10 immunoreactivity was illustrated [245]. Taken together, evidence strongly suggests a causative role for CXCL10 in the pathogenesis of AD, possibly extendable to other neurodegenerative disorders.

On the other hand, involvement of CXCL9 remains controversial as opposing reports regarding CXCL9 plasma levels in AD patients have been published [246, 247]. Additionally, considering the role of platelet activation, CXCL4 has also been suggested to support chronic inflammation in AD patients, though this hypothesis remains to be further investigated [248, 249].

3.13. Thrombocytopenia

Most of the CXCR3 ligands display a remarkable affinity for glycosaminoglycans, though none as outspoken as CXCL4. Glycosaminoglycans are believed to act as co-receptors for CXCR3 ligands, particularly in the process of leukocyte rolling and efficient tissue intravasation [250]. Yet the formation of CXCL4/heparin complexes upon administration of heparin as an anti-coagulant can also lead to a rare and paradoxical complication as the odd patient will develop antibodies against a CXCL4/heparin-epitope in the vicinity of the platelet surface [251]. This complication is referred to as heparin-induced thrombocytopenia (HIT). Patients developing HIT are at risk of venous as well as arterial thrombosis, despite low platelet counts [252].

4. CXCR3 LIGANDS IN THERAPY

A great range of pathologies, mostly characterized by inflammation or vascular effects, have clearly been associated with changes in the expression levels of CXCR3 and CXCR3-binding chemokines (summarized in Table 2). More importantly, often the expression of these chemokine ligands and receptor correlates to pathogenesis, disease progression and prognosis or, under particular conditions, could reflect a failing compensation mechanism. Insight into CXCR3 biology has consequently inspired the development of new therapeutics and continues to highlight new avenues worth exploring. Generally speaking, most CXCR3 axis-based therapies can be assigned to either the anti-inflammatory approach, by preventing CXCR3 activation, or an angiostatic approach, through the administration of exogenous CXCR3 ligands or peptides derived thereof. Possibly, this CXCR3 activation may also promote effective immune responses.

4.1. CXCR3 ligands as angiostatic and anti-tumoral therapeutics

Cancer is a prototypical angiogenic disorder in which neovascularization plays a crucial role in tumor progression and thus offers a promising therapeutic target. The angiostatic chemokines may represent an opportunity in the optimization of current anti-angiogenic regimes. Earlier in this review, we have elaborated on the anti-tumoral characteristics of CXCR3-binding chemokines, granted the malignant cells themselves do not express the CXCR3A splice variant. Though currently clinical use has not yet been tested, a wide selection of publications has discussed the benefits of CXCR3-based anti-tumoral strategies in various preclinical mouse models (Table 3).

Numerous experimental approaches have been described: different cancer models, combinations with other therapeutics, and administration strategies ranging from intratumoral chemokine injections to treatment with viral vectors [253]. Moreover, use of the CXCR3 ligands is also being fine-tuned by testing the impact of different alterations on their anti-tumoral activity. Carboxy-terminal peptides derived from the platelet factors [254, 255], even a chimeric chemokine integrating aspects of both CXCL10 and CXCL11 [256] or synthetic peptides such as anginex, which contains structural elements of CXCL4, CXCL8 as well as bactericidal permeability-increasing protein [257], have been tested to

optimize therapeutic efficacy (not included in table). Commonly, despite some exceptions, administration of CXCR3 ligands or derived preparations has shown innovative therapeutic benefit, holding promise for the future of anti-angiogenic cancer treatments.

Besides their application in cancer, administration of angiostatic chemokines like the CXCR3 ligands may also benefit patients suffering from many other angiogenic disorders, for example pathological ocular neovascularization in diabetic retinopathy.

4.2. CXCR3 ligands as targets in anti-inflammatory therapy

As IFN-γ-inducible, T cell-attracting chemokines, CXCL9, CXCL10 and CXCL11 most definitely play an important role in host immunity, yet they can also instigate endless amplification loops leading the way for excessive, detrimental immune responses [89]. Inflammatory disorders could benefit from anti-inflammatory agents inhibiting CXCR3 ligands and thereby breaking the cycle. Human monoclonal antibodies against CXCL10 have been developed for clinical use (MDX-1100/BMS-936557 and NI-0801; ClinicalTrials.gov). Thus far, use of the anti-CXCL10 antibody BMS-936557 has been examined in the treatment of IBD and RA patients and phase II trials have been completed reporting clinical efficacy in patients who previously responded inadequately to methotrexate [258, 259]. Treatment was generally well tolerated in both patient populations. Studies in cirrhosis patients are also ongoing, with a phase II trial just recently having been finalized (Study ID NCT01430429; ClinicalTrails.gov). CXCL10 could be considered the more clinically prominent of inflammatory CXCR3 ligands and therefore an obvious therapeutic target, however other chemokines of this group represent valuable alternatives. For example, CXCL4 takes on an interesting role in atherosclerosis and has been proposed as a promising therapeutic target as well [260, 261]. Other inflammatory disorders that may benefit from CXCR3 ligand blockade include type 1 diabetes, multiple sclerosis, allograft rejection, *etc.* [262, 263].

4.3. CXCR3 ligands as prognostic and predictive biomarkers

Finally, in many diseases, CXCR3 ligands provide an accessible readout for patient diagnosis, prognosis or therapy responsiveness. Prognostic significance of CXCL4L1 serum concentrations, for

example, was evidenced in stable coronary artery disease, in that lower CXCL4L1 levels were associated with a higher event rate and overall worse outcome [264]. In both Crohn's disease and RA, high plasma levels of CXCL4 have been shown to predict non-responsiveness to anti-TNFα antibody (infliximab) therapy [265, 266]. CXCR3 ligands have also been identified as crucial instigators of transplant inflammation and following allograft rejection [138]. Their expression, both pre- and post-transplantation, is a reflection of the patient's immune status. Urinary CXCL9 and CXCL10 have accordingly been described as useful, non-invasive biomarkers to predict or diagnose allograft rejection before overt clinical manifestation or irreversible graft injury [139, 146]. In the context of HCV, an association was noted between, on one hand, either intrahepatic or plasma levels of CXCL10 and, on the other hand, the patient's overall response to pegylated IFN-α2 and ribavirin combination therapy [267, 268]. Low baseline levels of CXCL10 proved to indicate a better outcome. These are just a few examples supporting the use of CXCR3 ligands as biomarkers to optimize individual treatment strategies.

Of note, interpretation of CXCL10 concentrations may be complicated considering recent reports on the detection of natural antagonistic forms of CXCL10, as observed in chronically HCV-infected patients [269]. Upon HCV infection, plasma CXCL10 is truncated by dipeptidyl peptidase IV (DPPIV)/CD26, generating its antagonistic form and thus interfering with its function as a pro-inflammatory leukocyte chemoattractant [270]. Amino-terminal truncation of the IFN-γ-inducible CXCR3 ligands by DPPIV was previously evidenced *in vitro* and indeed impaired their chemotactic activity, whilst retaining angiostatic potential [271]. Discovery of this functional difference between intact CXCL10 and its naturally occurring, amino-terminally processed form, challenges the significance of total, non-discriminatory CXCL10 concentrations detected in patients.

5. SUMMARY

CXCL4, CXCL4L1, CXCL9, CXCL10 and CXCL11 all bind, with varying affinity, to different splice variants of the CXCR3 receptor and are therefore collectively referred to as the CXCR3 ligands. Their pleiotropic character, regulating both leukocyte migration and angiogenesis, implicates these chemokines in a broad spectrum of diseases and their pathogenesis. Consequently, the CXCR3 ligands

have attracted attention as new therapeutic targets. However, the field is still lacking fundamental understanding of some of these chemokines. Ongoing research and clinical trials strive towards a better understanding of their basic biology, optimization of drug safety as well as efficacy. In conclusion, the CXCR3 ligands and their inhibitors represent a new generation of anti-angiogenic and anti-inflammatory strategies.

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FIGURE LEGENDS

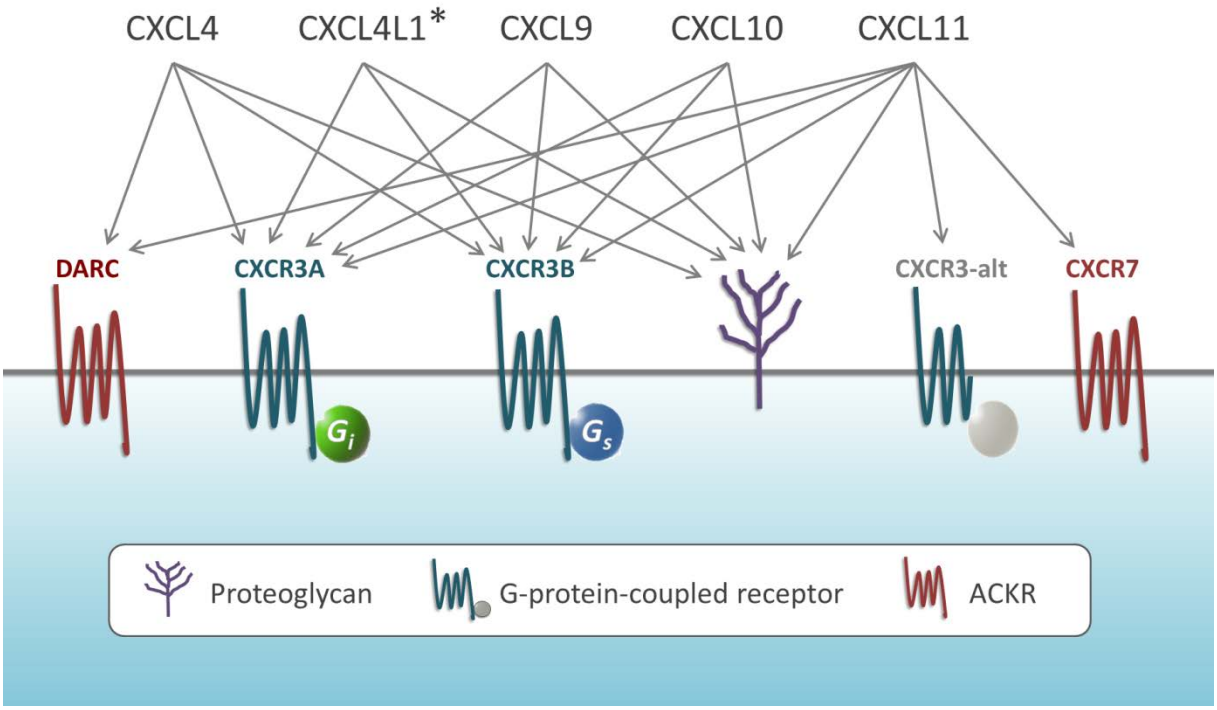

Fig. 1 Receptor binding by the IFN-γ-inducible chemokines, CXCL4 and CXCL4L1

CXCL4, CXCL4L1, CXCL9, CXCL10 and CXCL11, collectively acknowledged as the CXCR3 ligands, all bind both receptor splice variants CXCR3A and CXCR3B, whereas only CXCL11 binds the more distinctive CXCR3-alt [11-15]. CXCL11 also uniquely shows affinity for atypical chemokine receptor (ACKR) 3/CXCR7 [272]. On the other hand, both CXCL4 and CXCL11 bind to ACKR1/DARC [273, 274]. To some extent, all CXCR3-binding chemokines also display affinity for glycosaminoglycan branches on proteoglycans [16].

* Binding of CXCL4L1 to DARC has not yet been evaluated.

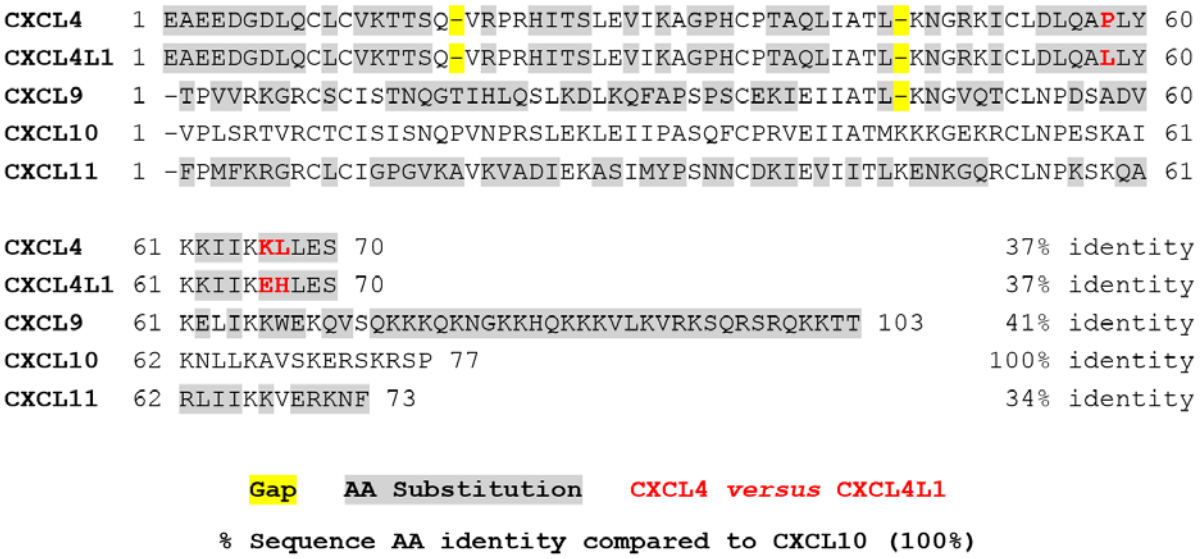

Fig. 2 Amino acid sequence alignment of the mature CXCR3-binding chemokines

The amino acid sequences of mature CXCL4, CXCL4L1, CXCL9 and CXCL11, without their respective signal peptides, were optimally aligned with respect to the mature CXCL10 chemokine. Their sequence identity compared to CXCL10 was calculated to give a general impression of the sequence homology among the CXCR3-binding chemokines. Mismatched amino acids (AA) are marked in grey. Gaps are marked in yellow. The differences between CXCL4 and CXCL4L1 are additionally marked in red.

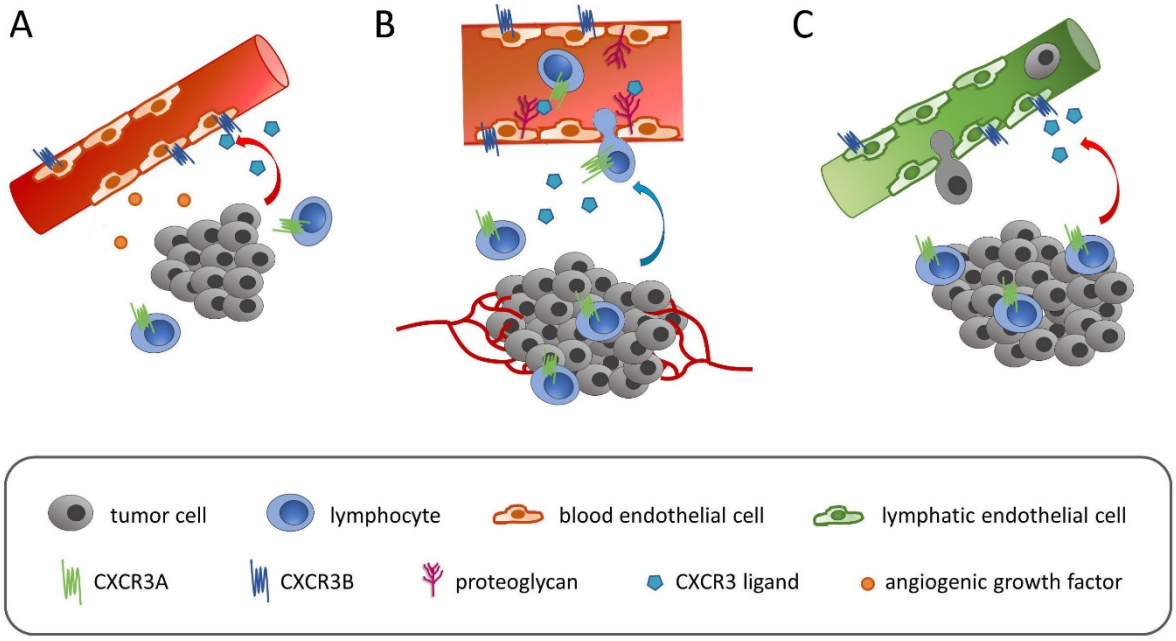

Fig. 3 The anti-tumoral activity of CXCR3 ligands

The CXCR3 ligands affect the tumor environment in various ways. Their anti-tumoral activity is the net result of their angiostatic effect, preventing tumor neovascularization (A), of the recruitment of pro-inflammatory lymphocytes, promoting tumor immunosurveillance (B), and finally, of their lymphangiostatic effect, preventing metastatic escape of tumor cells via the lymphatic vasculature (C) [31, 51].

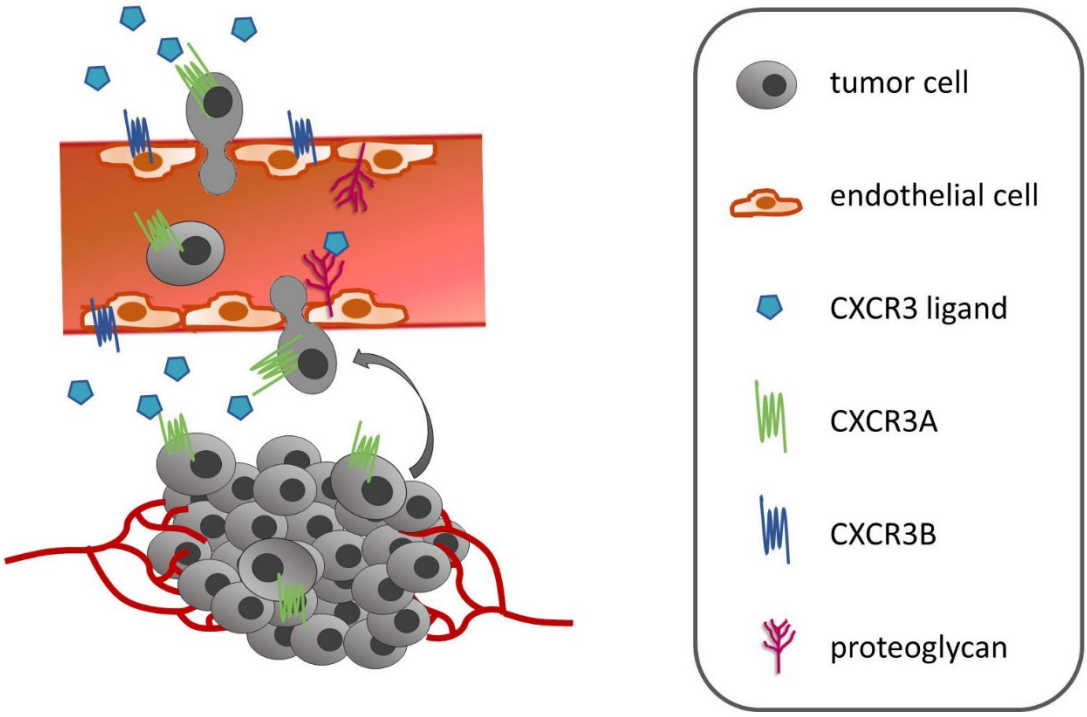

Fig. 4 The effect of CXCR3 ligands on tumor invasiveness

CXCR3 ligands may exert a direct effect on CXCR3-positive tumor cells, the nature of which depends on the specific splice variant expressed [59]. In case of CXCR3A expression, these chemokines will stimulate not only proliferation, but also migration of the CXCR3A-expressing tumor cells, especially to other peripheral sources of CXCR3 ligands, thereby promoting and directing tumor metastasis both to draining lymph nodes and distant organs, e.g. lung [275].

TABLES

Table 1. Fundamental characteristics of the human CXCR3 ligands

	CXCL4	**CXCL4L1**	**CXCL9**	**CXCL10**	**CXCL11**
Gene (HGNC)	NM_002619 4q13.3	NM_002620 4q13.3	NM_002416 4q21.1	NM_001565 4q21.1	NM_005409 4q21.1
Mature protein	70 AA	70 AA	103 AA	77 AA	73 AA
Producer cells	Platelets Monocytes T cells	Platelets Smooth muscle cells	HMVEC Fibroblasts Macrophages PBMC	HMVEC Fibroblasts Monocytes T cells Keratinocytes	HMVEC Fibroblasts Astrocytes PBMC
Inducers	Thrombin (platelets) Phorbol ester (T cells)	Thrombin (platelets)	IFN-γ	TNF-α (fibroblasts) IFN-α, IFN-β, IFN-γ	TNF-α (fibroblasts) IFN-γ, IFN-β
Processing					
- protease	N.D.	N.D.	DPPIV/CD26	DPPIV/CD26	DPPIV/CD26
- peptide product	CXCL4$^{17-70}$	. N.D	CXCL9 $^{3-103}$	CXCL10 $^{3-77}$	CXCL11 $^{3-73}$
- effect on:	N.D.		↓	↓	↓
chemotaxis	↑		=	=	=
angiostasis					
Ref	[44, 276]	[43, 44]	[37, 39, 41, 271]	[38-40, 271, 277]	[12, 39, 41, 271]

HGNC = HUGO gene nomenclature committee; AA = amino acids; N.D. = not determined; HMVEC = Human microvascular endothelial cell; PBMC = Peripheral blood mononuclear cell; TNF = Tumor necrosis factor; DPPIV = Dipeptidyl peptidase IV

Table 2. CXCR3 ligands in disease

Disease	CXCR3 ligand expression [a]	Function of CXCR3 ligands [b]
CANCER		
Carcinoma and sarcoma	↑ / ↓	Recruitment of anti-tumoral lymphocytes via CXCR3A (CXCL9, CXCL10, CXCL11) Angiostatic (all ligands) and lymphangiostatic (CXCL4, CXCL4L1) via CXCR3B
	↑	Increased tumor invasiveness via CXCR3A (CXCL4, CXCL10)
Hematopoietic malignancies	↑	Increased tumor cell dissemination (CXCL9, CXCL10, CXCL11) Anti-tumoral activity: tumor tissue necrosis, vascular damage, protective immune response (CXCL9, CXCL10)
	↓	Tumor suppressor gene (CXCL4)
INFLAMMATORY DISORDERS		
Arthritis	↑	Synovial inflammation (CXCL4, CXCL9, CXCL10) and vascular lesions (CXCL4)
IBD	↑	Mucosal inflammation (CXCL9, CXCL10, CXCL11)
Diabetes	↑	T cell islet infiltration (CXCL9, CXCL10) Decreased pancreatic beta cell proliferation (CXCL10) Correlation to angiogenic complication PDR (CXCL4, CXCL9, CXCL10)
Systemic sclerosis	↑	Fibrotic complications in the skin or lung (CXCL4, CXCL10)
	↓	Pulmonary function decline (CXCL11)
Transplant rejection	↑	Biomarkers predicting allograft failure (CXCL9, CXCL10, CXCL11)
	N.A.	Negative regulation of T cell reactivity (CXCL4)
MICROBIAL PATHOLOGIES		
Malaria	↑	Positive association with CM occurrence and mortality (CXCL4, CXCL9, CXCL10) CD8+ recruitment to the brain in murine CM (CXCL9, CXCL10)
	↑	Intraerythrocytic parasite-killing (CXCL4)
AIDS	↑	T cell recruitment and virus propagation (CXCL9, CXCL10, CXCL11) Stimulated virus replication (CXCL9, CXCL10, CXCL11) Inhibited host cell attachment and entry (CXCL4)
Hepatitis	↑	Lobular inflammation and liver fibrosis (CXCL4, CXCL9, CXCL10, CXCL11)
OTHER		
Atherosclerosis	↑	Lesional T cell infiltration (CXCL9, CXCL10, CXCL11) Monocyte recruitment and macrophage polarization (CXCL4) Promoted uptake and esterification of oxidized LDL (CXCL4)
Alzheimer's disease	↑	Promoted astrocyte aggregation (CXCL10) Neurotoxicity (CXCL10)
Thrombocytopenia	N.A.	Generation of antibodies against CXCL4/heparin complexes

IBD = Inflammatory bowel disease; PDR = Proliferative diabetic retinopathy; CM = Cerebral malaria; AIDS = Acquired immune deficiency syndrome; N.A. = Not applicable

[a] ↑ / ↓ = Upregulated or downregulated CXCR3 ligand expression, respectively, depending on the study

[b] For references *cfr*. citations in text

Table 3. Anti-tumoral effects of CXCR3 ligands: combination or monotherapies in preclinical models

Mouse model	CXCL4	CXCL4L1	CXCL9	CXCL10	CXCL11	Ref
B16 melanoma	✓	✓		✓		[278-282]
Lung adenocarcinoma (A11, A549, LLC)		✓	✓	✓		[278, 280, 283-286]
Colon adenocarcinoma (CT26, HCT116)	✓		✓	✓		[281, 284, 286, 287]
Capan-1 pancreatic adenocarcinoma		✓				[51]
Renal cell carcinoma (RENCA)			✓			[288]
Breast carcinoma (66.1, TA3)	✓		✓			[289, 290]
Ovarian carcinoma (SKOV3, ES2)	✓			✓		[290, 291]
Glioma (GL261, U87)	✓			✓		[292-294]
Malignant peripheral nerve sheath tumor	✓					[293, 295]
Meth A fibrosarcoma				✓		[296]
Angiosarcoma (H5V)				✓		[297]
Burkitt's lymphoma			✓			[298]
EL4 lymphoma					✓	[299]

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